REMARKS

Favorable reconsideration and allowance are respectfully requested. Claims 13-25 are pending. Claims 1-12 have been cancelled, without prejudice, as they are directed to non-elected subject matter. Several of the claims have been amended to correct informalities. For example, claims 13, 18, and 20 have been amended to correct their dependency from a claim which is no longer pending in this application. Moreover, claims 13 and 20 have been amended to recite information contained within that claim from which it formerly depended. Thus, these amendments do not constitute new matter. Therefore, claims 13-25 remain pending and at issue.

Objection to the Specification

The specification was objected to for failing to comply with the requirements for patent applications containing nucleotide sequences and/or amino acid sequence disclosures.

Accordingly, Applicant has amended Tables 1-6 and 8-9 to include the appropriate "SEQ ID NO" identifier for each sequence listed and to recite the three letter abbreviation for each amino acid listed in the sequences. Further, submitted herewith is a computer readable form copy of the Sequence Listing. Applicant submits that the content of the paper and computer readable copies are the same and do not include new matter.

Thus, reconsideration and withdrawal of the objection to the specification are respectfully requested.

Formal Objections to the Claims

Claims 13-25 were objected to for being in improper dependent form. Specifically, the Examiner objected to claim 18 for depending from later claim 19, and claims 13 and 20 were objected to for failing to further limit the subject matter of a previous, non-elected claim. Accordingly, Applicant has amended claim 18 to depend from claim 13, claims 1-12 have been cancelled, without prejudice, and claims 13 and 20 have been amended to be independent form. It is submitted that these claim amendments serve to obviate the formal objections to the claims.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 18, 13, 20 and 22 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to define that which Applicant regards as the invention.

Claim 18 was rejected for referring to "said analyte" without insufficient antecedent basis. Applicant has amended claim 18 to depend from claim 13, which should correct the antecedent basis for the term "said analyte".

Claim 22 was rejected for the recitation of "contacted with the chimeric first". Applicant has amended the claim to state that the analyte is contacted with the chimeric enzyme prior to contacting the chimeric enzyme with the test sample and the substrate.

Claims 13 and 20 were rejected for failing to recite a suitable control step which may be used to determine the amount of substrate catalysis observed in relation to that in the absence of the chimeric enzyme. Accordingly, Applicant has amended the claims to refer to a

comparison between the amount of catalysis of the substrate observed in the presence and absence of the chimeric enzyme.

Thus, it is submitted that the foregoing amendments obviate the Section 112, second paragraph rejections. Reconsideration and withdrawal of the Section 112, second paragraph, rejections are respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 13-25 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking an enabling disclosure. The Examiner alleges that the disclosure is enabling only for claims directed to a limited species of chimeric ß-lactamases. Specifically, the Examiner made the following observations:

> The claims are directed to a method for determining the presence of an analyte in a test sample using an enzyme as the starting enzyme, modifying the enzyme(s) to create a functional or enzymatically active chimeric enzyme having a binding site moiety, to which a binding molecule can attach. From the guidelines provided for construction of chimeric ß-lactamase and the skill of the artisan in the area of molecular biological and enzymology it would have been possible to make a number of single, double or multiple amino acid(s) modifications in the chimeric ß-lactamase structure in order to selectively modify the catalytic sites, to enable modulation upon binding. However, the transfer of such a construct to any amino acid modification within the ß-lactamase enzyme or any other enzyme in order to first produce a chimeric enzyme and further attempt to selectively insert or replace single, double or multiple amino acid inserts and develop chimeric enzyme binding site moiety which can successfully attach itself to a binding molecules, lacks adequate guidance, is unpredictable and would result in undue experimentation. . . . **In the absence of information regarding homologies and similarities between the exemplified enzyme and those from other groups, it remains unpredictable as to**

> **whether the disclosure concerning the instant ß-lactamase can be used to develop a method for determining analytes using other chimeric enzyme . . . [,] binding site moiety which can successfully attach itself to any binding molecules . . . , or where the analyte and substrate contact the enzyme simultaneously or in steps . . . , or where the test sample contains the analyte** . . . . (Official Action at 5-6).

Applicant respectfully traverses this rejection for the reasons outlined below.

Before specifically addressing the enablement rejection, it may be valuable to provide a brief overview of the present invention in order to place the enablement rejection in perspective. Briefly, as described on pages 2-9 of the subject specification, the present invention resides in the realization that one can modify the amino acid sequence of a starting enzyme by inserting the sequence of a mimetope in a sequence of the starting enzyme which is preferably remote from the active site of the enzyme. Alternatively, one can also modify the starting enzyme by replacing one or more amino acids in the sequence with that of the mimetope. Either of these modifications will result in a chimeric enzyme which retains the enzymatic activity, i.e., substrate specificity and/or catalytic activity, of the starting enzyme.

As discussed on page 10 of the subject specification, a mimetope is a determinant which is recognized by the same binding molecule as an epitope, but which has a different composition as the epitope, e.g., a different linear amino acid sequence which is still recognized by the same binding molecule. Thus, insertion of the mimetope sequence into that of the starting molecule will produce a chimeric enzyme which retains the activity of the starting molecule. Subsequently, a binding molecule binds to the chimeric enzyme and modulates the enzymatic activity in a detectable way, e.g., by either increasing or reducing the activity of the chimeric enzyme. Therefore, an analyte in a test sample may compete for

and/or displace the binding molecule from the chimeric enzyme, thereby reactivating it, and the reappearance of activity in the presence of the analyte indicates its existence and amount in the test sample.

Turning now to the instant rejections under Section 112, first paragraph, Applicant respectfully submits that one need **not** disclose each and every species within the claimed genus of β-lactamase enzymes in order to comply with the written description requirement. The Examiner has asserted that an applicant must disclose a representative number of species in order to provide an adequate written description of the genus, reasoning that when there is substantial variation within the genus, it may require a description of the various species to enable the claimed genus. However, the Examiner appears to be assuming his own conclusion: he has presumed that there ***is*** substantial variation in the sequence among the various species of β-lactamase. Such a conclusion must be supported by evidence and Applicant must be given the opportunity to address such evidence. The Examiner has not provided any evidence to support this conclusion. If he is aware of any evidence that would support his conclusion he is invited to present it so that Applicant may properly rebut the Examiner's conclusion. Alternatively, the Examiner is also invited to submit an Examiner's affidavit in support of his conclusions under 37 C.F.R. § 1.107. In the absence of such supporting evidence, the rejection is untenable and should be withdrawn.

Even if there is variation among the species that comprise the genus, although such is not admitted here, it is of no moment because the disclosure provides sufficient guidance to the skilled artisan to prepare a chimeric enzyme given any starting enzyme. As discussed above, the present invention entails inserting or replacing the amino acid sequence of a starting

enzyme with that of a mimetope in a position of the sequence of the starting enzyme which is preferably *remote* from the active site of the enzyme. Once the target molecule is selected, a library of mimetopes may be created and engineered, e.g., inserted, into the sequence of the target molecule, in a position which is preferably remote from the active site, and the resultant chimeric molecule is screened and selected for retention of activity (Specification at 11). Thus, using a library of mimetopes and routine screening methods available to those skilled in the art, one need not know the structure of the epitope to practice the instant invention; nor would one need to have specific information about the sequence homology or functional similarity among different enzymes in order to modify a starting enzyme and screen for the desired activity.

While this method has been demonstrated using a particular species of β-lactamase enzymes, it is generally applicable to a broad range of starting molecules, such as, β-lactamase, plasmin, prostate specific antigen, subtilisin, alkaline phosphatase, β-galactosidase, *S. nuclease*, glutathione transferase, lysozyme, a catalytic antibody, esterases, pyruvate kinase, glucose oxidase, lactate dehydrogenase, glucose 6-phosphate dehydrogenase or luciferase (Specification at 2-3). With each starting molecule, one would create a library of mimetopes, and screen the library for biological activity. One can identify a chimera that retains the activity of the starting enzyme with only routine screening and without undue experimentation.

Further, one must also consider the fact that the level of skill in the art is high. Given the extensive guidance available to the skilled artisan in the subject specification, together with that generally known by those skilled in the art of genetic engineering and molecular biology, and more specifically, that which is already known about the sequence homology and

functional similarity among the different enzymes or molecules which are listed in the subject specification, one skilled in the art could readily prepare a chimeric molecule using any starting molecule, in accordance with the instant invention, without undue experimentation. Contrary to these assertions, the Examiner maintains, without any evidence to support his conclusion, that the genus ß-lactamase includes a diverse number of enzymes, presumably having dissimilar sequence homologies and functional similarities, and that in order to enable the preparation of a chimeric enzyme using any ß-lactamase, Applicant must enable a representative number of species within the genus. As discussed above, Applicant has enabled the general method of preparing a chimeric enzyme, which is equally applicable to any starting molecule. Applicant has also demonstrated this method with a particular species of ß-lactamase. Nevertheless, the Examiner asserts that this is insufficient.

However, the Examiner has failed to consider the fact that much is known about the genus ß-lactamase and was known as of the filing date of the instant application. For example, as shown in the accompanying literature references, Livermore, "ß-Lactamases in Laboratory and Clinical Resistance", Clinical Microbiology Reviews, 8(4): 557-584 (1995) ("Livermore"), and Bush et al., "A Functional Classification Scheme for ß-Lactamases and Its Correlation with Molecular Structure", Antimicrobial Agents and Chemotherapy, 39(6): 1211-1233 (1995) ("Bush"), a great deal of functional and sequence information is known about this genus of enzymes. For example, at page 1216, Bush states that "[t]he complete nucleotide or amino acid sequence of many ß-lactamases has now been determined. A dendrogram expressing the molecular relationship among **88** enzymes classified in Tables 2 to 11 was constructed by the progressive alignment method . . . " (emphasis added). While there may be some diversity in

the number of amino acid substitutions that can be tolerated by a given species, much is known about that diversity, and the skilled artisan would have ample information in order to ascertain whether any given substitution will be tolerated. (However, as discussed above, one need not know this level of detail before creating a library of mimetopes because those modifications which are not tolerated will be immediately identified in the screening method.)

Further, the invention is equally applicable to other enzymes, including, but not limited to, plasmin, prostate specific antigen, subtilisin, alkaline phosphatase, β-galactosidase, *S. nuclease*, glutathione transferase, lysozyme, a catalytic antibody, esterases, pyruvate kinase, glucose oxidase, lactate dehydrogenase, glucose 6-phosphate dehydrogenase or luciferase (Specification at 2-3). Attached is a list of the sequence information available for a variety of these classes of enzymes which is publicly available through one of many sequence databases (see e.g., http://www-nbrf.georgetown.edu). In addition to the amino acid and nucleotide sequences for a variety of the species for each class of enzyme, one may also perform sequence alignments and get information about the sequence homology among the difference species within a genus of enzymes. Clearly, there is a plethora of information available concerning the enzymes which have been described in the instant specification, and the skilled artisan would not have to resort to undue experimentation to reduce the invention to practice.

Based on the extensive guidance provided in the instant disclosure, such as the examples which illustrate the invention using one of many starting enzymes, all that would be required of the skilled artisan to practice the instant invention is to identify a starting material, prepare a library of mimetopes and insert the sequences into the starting material, and screen

for activity. Enablement is not precluded by the necessity for experimentation such as routine screening. *See supra, In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Thus, it is respectfully submitted that the skilled artisan would not need to experiment extensively to reduce the instant invention to practice. Therefore, the full scope of the claims are sufficiently enabled by the instant disclosure, and favorable reconsideration and withdrawal of the Section 112, first paragraph rejections are respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 13-14, 16-25 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Rodriques et al. (Cancer Research, 55: 63-70 (1995); "Rodriques"). The Examiner asserted that because Rodriques describes all the elements of the claims, the reference anticipates the claims.

Applicant respectfully traverses the Section 102 rejection.

In order for a reference to anticipate a claim, that reference must contain all of the elements of the claim. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986); *In re Marshall*, 578 F.2d 301, 304 (C.C.P.A. 1978). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

With this standard in mind, Applicant would like to highlight the elements of claims 13 and 20, for ease of reference.

- a chimeric enzyme which has the same enzymatic activity as that of the starting enzyme;
- a starting enzyme comprising a polypeptide;
- a mimetope inserted into the sequence of the starting enzyme or which replaces at least one amino acid in the sequence of the starting enzyme; and
- the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the mimetope.

Rodriques relates to the attachment of a portion of an antibody to β-lactamase as a targeting agent for use in targeted prodrug therapy. Rather than inserting a mimetope sequence into the sequence of the starting enzyme or replacing a segment of the starting enzyme sequence with the mimetope, which mimetope is recognized by a binding molecule, Rodriques attaches an antibody, i.e., a binding molecule, directly to the starting enzyme to produce a fusion protein. The instant claims specifically require insertion of a mimetope into a starting enzyme, which is recognized and binds to a binding molecule. The attachment of the binding molecule to the chimeric enzyme modulates the activity of the chimeric enzyme. In contrast, Rodriques attaches the binding molecule (an antibody) directly to the starting enzyme and there is no modulation of the chimeric enzyme's activity as a result of an interaction between the chimeric enzyme and a separate binding molecule, which is not incorporated into the sequence of the chimeric enzyme.

Thus, Rodriques fails to disclose at least two elements of the instant claims, i.e., (1) a mimetope inserted into the sequence of the starting enzyme or which replaces at least one amino acid in the sequence of the starting enzyme, and (2) the activity of the chimeric enzyme

is modulated upon binding of a binding molecule to the mimetope. Hence, the Rodriques fails to anticipate the claims and the Section 102 rejection should be withdrawn.

Therefore, favorable reconsideration and withdrawal of the Section 102 rejections are warranted.

* * *

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the claims are in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

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